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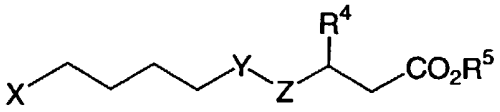
(54) Title: ALPHA V INTEGRIN RECEPTOR ANTAGONISTS

(57) Abstract: The present invention relates to novel alkanoic acid derivatives thereof, their synthesis, and their use as αv integrin receptor antagonists. More particularly, the compounds of the present invention are antagonists of the integrin receptors αvβ3 and/or αβ5 and are useful for inhibiting bone resorption, treating and preventing osteoporosis, and inhibiting vascular restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammatory arthritis, cancer, and metastatic tumor growth.

WHAT IS CLAIMED IS:

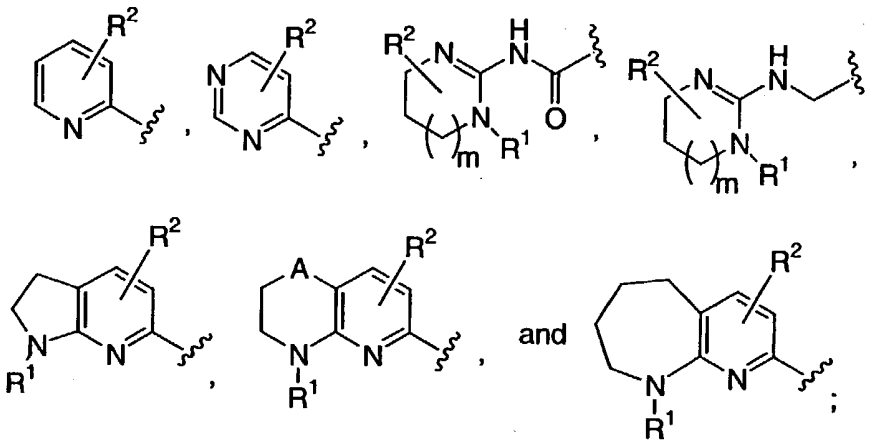
1. A compound of the Formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X is selected from the group consisting of



Y-Z is $-CH_2CH_2-$ or $-CONR^3-$;

A is O or NR^1;

m is 0 or 1;

R^1 is hydrogen or C_{1-3} alkyl;

each non-aromatic ring carbon atom is unsubstituted or independently substituted with one or two R^2 substituents and each aromatic ring carbon atom is unsubstituted or independently substituted with one R^2 substituent selected from the group consisting of

C_{1-8} alkyl, C_{3-8} cycloalkyl,
C_{3-8} cycloheteroalkyl, C_{3-8} cycloalkyl-C_{1-6} alkyl,
C_{3-8} cycloheteroalkyl-C_{1-6} alkyl, aryl, aryl-C_{1-6} alkyl, amino,
amino-C_{1-6} alkyl, C_{1-3} acylamino, C_{1-3} acylamino-C_{1-6} alkyl,
(C_{1-6} alkyl)$_{1-2}$ amino, C_{3-6} cycloalkyl-C_{0-2} amino,
(C_{1-6} alkyl)$_{1-2}$ amino-C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-4} alkoxy-C_{1-6} alkyl,
hydroxycarbonyl, hydroxycarbonyl-C_{1-6} alkyl, C_{1-3} alkoxycarbonyl,
C_{1-3} alkoxycarbonyl-C_{1-6} alkyl, hydroxy, hydroxy-C_{1-6} alkyl,
nitro, cyano, trifluoromethyl, trifluoromethoxy, trifluoroethoxy,
C_{1-8} alkyl-S(O)$_{0-2}$, (C_{1-8} alkyl)$_{0-2}$ aminocarbonyl,
C_{1-8} alkyloxycarbonylamino, (C_{1-8} alkyl)$_{1-2}$ aminocarbonyloxy,
(aryl C_{1-3} alkyl)$_{1-2}$ amino, (aryl)$_{1-2}$ amino,
aryl-C_{1-3} alkylsulfonylamino, and C_{1-8} alkylsulfonylamino;

or two R^2 substituents, when on the same non-aromatic carbon atom, are taken together with the carbon atom to which they are attached to form a carbonyl group, or two R^2 substituents, together with the carbon atoms to which they are attached, join to form a 3- to 6-membered saturated spiro-carbocyclic ring;

R^3 is hydrogen or C_{1-4} alkyl;

R^4 is aryl wherein the aryl group is selected from the group consisting of

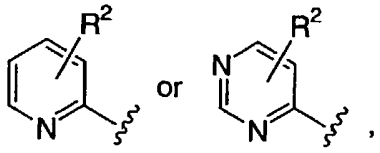
(1) phenyl,
(2) naphthyl,
(3) pyridinyl,
(4) furyl,
(5) thienyl,
(6) pyrrolyl,
(7) oxazolyl,
(8) thiazolyl,
(9) imidazolyl,
(10) pyrazolyl,
(11) isoxazolyl,
(12) isothiazolyl,
(13) pyrimidinyl,

(14) pyrazinyl,
(15) pyridazinyl,
(16) quinolyl,
(17) isoquinolyl,
(18) benzimidazolyl,
(19) benzofuryl,
(20) benzothienyl,
(21) indolyl,
(22) benzthiazolyl,
(23) benzoxazolyl,
(24) dihydrobenzofuryl,
(25) benzo(1,3)dioxolanyl,
(26) benzo(1,4)dioxanyl, and
(27) quinoxalinyl;

and mono, di, and tri-substituted aryl wherein the substituents are independently hydrogen, hydroxy, hydroxy-C_{1-6} alkyl, halogen, C_{1-8} alkyl, C_{3-8} cycloalkyl, aryl, aryl C_{1-3} alkyl, amino, amino C_{1-6} alkyl, C_{1-3} acylamino, C_{1-3} acylamino-C_{1-6} alkyl, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkylamino-C_{1-6} alkyl, di(C_{1-6})alkylamino-C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkoxy-C_{1-6} alkyl, hydroxycarbonyl, hydroxycarbonyl-C_{1-6} alkyl, C_{1-5} alkoxycarbonyl, C_{1-3} alkoxycarbonyl-C_{1-6} alkyl, C_{1-5} alkylcarbonyloxy, cyano, trifluoromethyl, 1,1,1-trifluoroethyl, trifluoromethoxy, trifluoroethoxy, or nitro; or two adjacent substituents together with the carbon atoms to which they are attached join to form a five- or six-membered saturated or unsaturated ring containing 1 or 2 heteroatoms selected from the group consisting of N, O, and S, whose ring carbon atoms may be substituted with oxo or C_{1-3} alkyl; and

R^5 is hydrogen or C_{1-3} alkyl.

2. The compound of Claim 1 wherein X is selected from the group consisting of



Y is $-CH_2CH_2-$; and

R^2, R^4, and R^5 are as defined in Claim 1.

3. The compound of Claim 2 wherein R^4 is mono- or di-substituted

phenyl,
pyridinyl,
quinolyl,
pyrimidinyl,
pyrazinyl,
quinoxalinyl, or
dihydrobenzofuryl;

wherein the substituents are independently hydrogen, hydroxy, hydroxy-C_{1-6} alkyl,. halogen, C_{1-8} alkyl, C_{3-8} cycloalkyl, aryl, aryl C_{1-3} alkyl, amino, amino-C_{1-6} alkyl, C_{1-3} acylamino, C_{1-3} acylamino-C_{1-6} alkyl, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkylamino C_{1-6} alkyl, di(C_{1-6})alkylamino-C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkoxy-C_{1-6} alkyl, hydroxycarbonyl, hydroxycarbonyl-C_{1-6} alkyl, C_{1-5} alkoxycarbonyl, C_{1-3} alkoxycarbonyl C_{1-6} alkyl, C_{1-5} alkylcarbonyloxy, cyano, trifluoromethyl, 1,1,1-trifluoroethyl, trifluoromethoxy, trifluoroethoxy, or nitro; or two adjacent substituents together with the carbon atoms to which they are attached join to form a five- or six-membered saturated or unsaturated ring containing 1 or 2 heteroatoms selected from the group consisting of N, O, and S, whose ring carbon atoms may be substituted with oxo or C_{1-3} alkyl.

4. The compound of Claim 3 wherein R^4 is mono- or di-substituted

pyridinyl,

quinolyl,
pyrimidinyl,
pyrazinyl,
quinoxalinyl, or
dihydrobenzofuryl;

wherein the substituents are independently hydrogen, halogen, phenyl, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy, amino, C_{1-3} alkylamino, di(C_{1-3}) alkylamino, hydroxy, cyano, trifluoromethyl, 1,1,1-trifluoroethyl, trifluoromethoxy, or trifluoroethoxy.

5. The compound of Claim 4 wherein R^2 is selected from the group consisting of
hydrogen,
amino,
C_{1-4} alkylamino,
C_{3-6} cycloalkyl-C_{0-2} alkylamino
cyano,
C_{1-4} alkyl,
cyclopropyl,
aryl C_{1-3} alkyl,
C_{1-4} acylamino,
C_{1-4} alkoxy,
C_{1-4} alkylthio,
aminocarbonyl,
(C_{1-6} alkyl)$_{1-2}$ aminocarbonyl,
C_{1-4} alkoxycarbonyl,
trifluoromethyl, and
trifluoromethoxy.

6. The compound of Claim 5 wherein R^2 is selected from the group consisting of
hydrogen,
amino,
C_{1-3} alkylamino,

C_{3-6} cycloalkylmethylamino,
C_{1-4} alkyl,
cyclopropyl,
trifluoromethyl, and
trifluoromethoxy.

7. The compound of Claim 1 selected from the group consisting of:

{[5-(2,4-Diaminopyrimidin-6-yl)pentanoyl]-(N-methyl)amino}-3-(6-methoxypyridin-3-yl)-propanoic acid;

{[5-(2,4-Diaminopyrimidin-6-yl)pentanoyl]-(N-methyl)amino-3(R)-(6-methoxypyridin-3-yl)-propanoic acid;

{[5-(2,4-Diaminopyrimidin-6-yl)pentanoyl]-(N-methyl)amino-3(S)-(6-methoxypyridin-3-yl)-propanoic acid;

{[5-(3-Amino-5,6,7,8-tetrahydroisoquinolin-1-yl)pentanoyl]-(N-methyl)amino}-3-(6-methoxypyridin-3-yl)-propanoic acid;

{[5-(3-Amino-5,6,7,8-tetrahydroisoquinolin-1-yl)pentanoyl]-(N-methyl)amino}-3(R)-(6-methoxypyridin-3-yl)-propanoic acid;

{[5-(3-Amino-5,6,7,8-tetrahydroisoquinolin-1-yl)pentanoyl]-(N-methyl)amino}-3(S)-(6-methoxypyridin-3-yl)-propanoic acid;

3-(5-3,4-Dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl-pentanoylamino)-3-(quinolin-3-yl)-propionic acid;

3-(5-3,4-Dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl-pentanoylamino)-3(R)-(quinolin-3-yl)-propionic acid;

3-(5-3,4-Dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl-pentanoylamino)-3(S)-(quinolin-3-yl)-propionic acid;

3-(Quinolin-3-yl)-3-(5-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazin-6-yl-pentanoylamino)-propionic acid;

3(R)-(Quinolin-3-yl)-3-(5-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazin-6-yl-pentanoylamino)-propionic acid;

3(S)-(Quinolin-3-yl)-3-(5-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazin-6-yl-pentanoylamino)-propionic acid;

9-(6-Methylamino-pyridin-2-yl)-3-(pyrimidin-5-yl)-nonanoic acid;

9-(6-Methylamino-pyridin-2-yl)-3(R)-(pyrimidin-5-yl)-nonanoic acid;

9-(6-Methylamino-pyridin-2-yl)-3(S)-(pyrimidin-5-yl)-nonanoic acid;

9-(2,4-Diaminopyrimidin-6-yl)-3-(quinolin-3-yl)-nonanoic acid;

9-(2,4-Diaminopyrimidin-6-yl)-3(R)-(quinolin-3-yl)-nonanoic acid;

9-(2,4-Diaminopyrimidin-6-yl)-3(S)-(quinolin-3-yl)-nonanoic acid;

3(2-Methyl-pyrimidin-5-yl)-9-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

3(R)-(2-Methyl-pyrimidin-5-yl)-9-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

3(S)-(2-Methyl-pyrimidin-5-yl)-9-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

3-Pyrimidin-5-yl-9-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

3(R)-Pyrimidin-5-yl-9-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

3(S)-Pyrimidin-5-yl-9-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

(2-Methyl-pyrimidin-5-yl)-9-(1,4,5,6-tetrahydro-pyrimidin-2-ylcarbamoyl)-nonanoic acid;

3(R)-(2-Methyl-pyrimidin-5-yl)-9-(1,4,5,6-tetrahydro-pyrimidin-2-ylcarbamoyl)-nonanoic acid;

3(S)-(2-Methyl-pyrimidin-5-yl)-9-(1,4,5,6-tetrahydro-pyrimidin-2-ylcarbamoyl)-nonanoic acid;

9-(6-Methylamino-pyridin-2-yl)-3-(2-methyl-pyrimidin-5-yl)-nonanoic acid;

9-(6-Methylamino-pyridin-2-yl)-3(R)-(2-methyl-pyrimidin-5-yl)-nonanoic acid;

9-(6-Methylamino-pyridin-2-yl)-3(S)-(2-methyl-pyrimidin-5-yl)-nonanoic acid;

3-(2-Methoxy-pyrimidin-5-yl)-9-(6-methylamino-pyridin-2-yl)-nonanoic acid;

3(R)-(2-Methoxy-pyrimidin-5-yl)-9-(6-methylamino-pyridin-2-yl)-nonanoic acid;

3(S)-(2-Methoxy-pyrimidin-5-yl)-9-(6-methylamino-pyridin-2-yl)-nonanoic acid;

3-(2-Ethoxy-pyrimidin-5-yl)-9-(6-methylamino-pyridin-2-yl)-nonanoic acid;

3(R)-(2-Ethoxy-pyrimidin-5-yl)-9-(6-methylamino-pyridin-2-yl)-nonanoic acid;

3(S)-(2-Ethoxy-pyrimidin-5-yl)-9-(6-methylamino-pyridin-2-yl)-nonanoic acid;

9-(6-Ethylamino-pyridin-2-yl)-3-(2-methyl-pyrimidin-5-yl)-nonanoic acid;

9-(6-Ethylamino-pyridin-2-yl)-3(R)-(2-methyl-pyrimidin-5-yl)-nonanoic acid;

9-(6-Ethylamino-pyridin-2-yl)-3(S)-(2-methyl-pyrimidin-5-yl)-nonanoic acid;

3-(2-Methoxy-pyrimidin-5-yl)-9-(6-ethylamino-pyridin-2-yl)-nonanoic acid;

3(R)-(2-Methoxy-pyrimidin-5-yl)-9-(6-ethylamino-pyridin-2-yl)-nonanoic acid;

3(S)-(2-Methoxy-pyrimidin-5-yl)-9-(6-ethylamino-pyridin-2-yl)-nonanoic acid;

3-(2-Ethoxy-pyrimidin-5-yl)-9-(6-ethylamino-pyridin-2-yl)-nonanoic acid;

3(R)-(2-Ethoxy-pyrimidin-5-yl)-9-(6-ethylamino-pyridin-2-yl)-nonanoic acid;

3(S)-(2-Ethoxy-pyrimidin-5-yl)-9-(6-ethylamino-pyridin-2-yl)-nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3-(dihydrobenzofuran-6-yl)-nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(R)-(dihydrobenzofuran-6-yl)-nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(S)-(dihydrobenzofuran-6-yl)-nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3-(6-methoxypyridin-3-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(R)-(6-methoxypyridin-3-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(S)-(6-methoxypyridin-3-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3-(2-methoxypyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(R)-(2-methoxypyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(S)-(2-methoxypyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3-(2-ethoxypyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(R)-(2-ethoxypyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(S)-(2-ethoxypyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3-(2-methylpyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(R)-(2-methylpyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(S)-(2-methylpyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3-(quinoxalin-2-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(R)-(quinoxalin-2-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(S)-(quinoxalin-2-yl)nonanoic acid;

9-(2-Amino-4-ethylaminopyrimidin-6-yl)-3-(2-ethoxypyrimidin-5-yl)nonanoic acid;

9-(2-Amino-4-ethylaminopyrimidin-6-yl)-3(R)-(2-ethoxypyrimidin-5-yl)nonanoic acid;

9-(2-Amino-4-ethylaminopyrimidin-6-yl)-3(S)-(2-ethoxypyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-aminopyrimidin-6-yl)-3-(2-methylpyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-aminopyrimidin-6-yl)-3(R)-(2-methylpyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-aminopyrimidin-6-yl)-3(S)-(2-methylpyrimidin-5-yl)nonanoic acid;

9-(2-Ethylaminopyrimidin-6-yl)-3-(2-ethoxypyrimidin-5-yl)nonanoic acid;

9-(2-Ethylaminopyrimidin-6-yl)-3(R)-(2-ethoxypyrimidin-5-yl)nonanoic acid;

9-(2-Ethylaminopyrimidin-6-yl)-3(S)-(2-ethoxypyrimidin-5-yl)nonanoic acid;

9-(6-Methylamino-pyridin-2-yl)-3-quinoxalin-2-yl-nonanoic acid;

3(R)-9-(6-Methylamino-pyridin-2-yl)-3-quinoxalin-2-yl-nonanoic acid;

3(S)-9-(6-Methylamino-pyridin-2-yl)-3-quinoxalin-2-yl-nonanoic acid;

9-(2,3-Dihydro-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-methyl-pyrimidin-5-yl)-nonanoic acid;

3(R)-9-(2,3-Dihydro-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-methyl-pyrimidin-5-yl)-nonanoic acid;

3(S)-9-(2,3-Dihydro-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-methyl-pyrimidin-5-yl)-nonanoic acid; and

3-(2-Methyl-pyrimidin-5-yl)-10-(1,4,5,6-tetrahydro-pyrimidin-2-ylamino)-decanoic acid;

or a pharmaceutically acceptable salt thereof.

8. The compound of Claim 7 selected from the group consisting of:

{[5-(2,4-Diaminopyrimidin-6-yl)pentanoyl]-(N-methyl)amino-3(R)-(6-methoxypyridin-3-yl)-propanoic acid;

{[5-(2,4-Diaminopyrimidin-6-yl)pentanoyl]-(N-methyl)amino-3(S)-(6-methoxypyridin-3-yl)-propanoic acid;

{[5-(3-Amino-5,6,7,8-tetrahydroisoquinolin-1-yl)pentanoyl]-(N-methyl)amino}-3(R)-(6-methoxypyridin-3-yl)-propanoic acid;

{[5-(3-Amino-5,6,7,8-tetrahydroisoquinolin-1-yl)pentanoyl]-(N-methyl)amino}-3(S)-(6-methoxypyridin-3-yl)-propanoic acid;

3-(5-3,4-Dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl-pentanoylamino)-3(R)-(quinolin-3-yl)-propionic acid;

3-(5-3,4-Dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl-pentanoylamino)-3(S)-(quinolin-3-yl)-propionic acid;

3(R)-(Quinolin-3-yl)-3-(5-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazin-6-yl-pentanoylamino)-propionic acid;

3(S)-(Quinolin-3-yl)-3-(5-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazin-6-yl-pentanoylamino)-propionic acid;

9-(6-Methylamino-pyridin-2-yl)-3(R)-(pyrimidin-5-yl)-nonanoic acid;

9-(6-Methylamino-pyridin-2-yl)-3(S)-(pyrimidin-5-yl)-nonanoic acid;

9-(2,4-Diaminopyrimidin-6-yl)-3(R)-(quinolin-3-yl)-nonanoic acid;

9-(2,4-Diaminopyrimidin-6-yl)-3(S)-(quinolin-3-yl)-nonanoic acid;

3(R)-(2-Methyl-pyrimidin-5-yl)-9-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

3(S)-(2-Methyl-pyrimidin-5-yl)-9-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

3(R)-Pyrimidin-5-yl-9-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

3(S)-Pyrimidin-5-yl-9-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

3(R)-(2-Methyl-pyrimidin-5-yl)-9-(1,4,5,6-tetrahydro-pyrimidin-2-ylcarbamoyl)-nonanoic acid;

3(S)-(2-Methyl-pyrimidin-5-yl)-9-(1,4,5,6-tetrahydro-pyrimidin-2-ylcarbamoyl)-nonanoic acid;

9-(6-Methylamino-pyridin-2-yl)-3(R)-(2-methyl-pyrimidin-5-yl)-nonanoic acid;

9-(6-Methylamino-pyridin-2-yl)-3(S)-(2-methyl-pyrimidin-5-yl)-nonanoic acid;

3(R)-(2-Methoxy-pyrimidin-5-yl)-9-(6-methylamino-pyridin-2-yl)-nonanoic acid;

3(S)-(2-Methoxy-pyrimidin-5-yl)-9-(6-methylamino-pyridin-2-yl)-nonanoic acid;

3(R)-(2-Ethoxy-pyrimidin-5-yl)-9-(6-methylamino-pyridin-2-yl)-nonanoic acid;

3(S)-(2-Ethoxy-pyrimidin-5-yl)-9-(6-methylamino-pyridin-2-yl)-nonanoic acid;

9-(6-Ethylamino-pyridin-2-yl)-3(R)-(2-methyl-pyrimidin-5-yl)-nonanoic acid;

9-(6-Ethylamino-pyridin-2-yl)-3(S)-(2-methyl-pyrimidin-5-yl)-nonanoic acid;

3(R)-(2-Methoxy-pyrimidin-5-yl)-9-(6-ethylamino-pyridin-2-yl)-nonanoic acid;

3(S)-(2-Methoxy-pyrimidin-5-yl)-9-(6-ethylamino-pyridin-2-yl)-nonanoic acid;

3(R)-(2-Ethoxy-pyrimidin-5-yl)-9-(6-ethylamino-pyridin-2-yl)-nonanoic acid;

3(S)-(2-Ethoxy-pyrimidin-5-yl)-9-(6-ethylamino-pyridin-2-yl)-nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(R)-(dihydrobenzofuran-6-yl)-nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(S)-(dihydrobenzofuran-6-yl)-nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(R)-(6-methoxypyridin-3-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(S)-(6-methoxypyridin-3-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(R)-(2-methoxypyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(S)-(2-methoxypyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(R)-(2-ethoxypyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(S)-(2-ethoxypyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(R)-(2-methylpyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(S)-(2-methylpyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(R)-(quinoxalin-2-yl)nonanoic acid;

9-(4-Amino-2-ethylaminopyrimidin-6-yl)-3(S)-(quinoxalin-2-yl)nonanoic acid;

9-(2-Amino-4-ethylaminopyrimidin-6-yl)-3(R)-(2-ethoxypyrimidin-5-yl)nonanoic acid;

9-(2-Amino-4-ethylaminopyrimidin-6-yl)-3(S)-(2-ethoxypyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-aminopyrimidin-6-yl)-3(R)-(2-methylpyrimidin-5-yl)nonanoic acid;

9-(4-Amino-2-aminopyrimidin-6-yl)-3(S)-(2-methylpyrimidin-5-yl)nonanoic acid;

9-(2-Ethylaminopyrimidin-6-yl)-3(R)-(2-ethoxypyrimidin-5-yl)nonanoic acid;

9-(2-Ethylaminopyrimidin-6-yl)-3(S)-(2-ethoxypyrimidin-5-yl)nonanoic acid;

3(R)-9-(6-Methylamino-pyridin-2-yl)-3-quinoxalin-2-yl-nonanoic acid;

3(S)-9-(6-Methylamino-pyridin-2-yl)-3-quinoxalin-2-yl-nonanoic acid;

3(R)-9-(2,3-Dihydro-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-methyl-pyrimidin-5-yl)-nonanoic acid; and

3(S)-9-(2,3-Dihydro-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-methyl-pyrimidin-5-yl)-nonanoic acid;

or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier.

10. The composition of Claim 9 which further comprises an active ingredient selected from the group consisting of

a) an organic bisphosphonate or a pharmaceutically acceptable salt or ester thereof,

b) an estrogen receptor modulator,
c) an androgen receptor modulator,
d) a cytotoxic/antiproliferative agent,
e) a matrix metalloproteinase inhibitor,
f) an inhibitor of epidermal-derived, fibroblast-derived, or platelet-derived growth factors,
g) an inhibitor of VEGF,
h) an antibody to a growth factor or a growth factor receptor,
i) an inhibitor of Flk-1/KDR, Flt-1, Tck/Tie-2, or Tie-1,
j) a cathepsin K inhibitor,
k) a growth hormone secretagogue,
l) an inhibitor of osteoclast proton ATPase,
m) an inhibitor of urokinase plasminogen activator (u-PA),
n) a tumor-specific antibody-interleukin-2 fusion protein,
o) an inhibitor of HMG-CoA reductase, and
p) a farnesyl transferase inhibitor or a geranylgeranyl transferase inhibitor or a dual farnesyl/geranylgeranyl transferase inhibitor;
and mixtures thereof.

11. The composition of Claim 10 wherein said active ingredient is selected from the group consisting of

a) an organic bisphosphonate or a pharmaceutically acceptable salt or ester thereof,
b) an estrogen receptor modulator,
c) an androgen receptor modulator,
d) a cathepsin K inhibitor,
e) an HMG-CoA reductase inhibitor, and
f) an inhibitor of osteoclast proton ATPase;
and mixtures thereof.

12. The composition of Claim 11 wherein said organic bisphosphonate or pharmaceutically acceptable salt or ester thereof is alendronate monosodium trihydrate.

13. A method of eliciting an αv integrin receptor antagonizing effect in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a compound according to Claim 1.

14. The method of Claim 13 wherein αv the integrin receptor antagonizing effect is an αvβ3 antagonizing effect.

15. The method of Claim 14 wherein the αvβ3 antagonizing effect is selected from the group consisting of inhibition of bone resorption, restenosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammatory arthritis, cancer, and metastatic tumor growth.

16. The method of Claim 15 wherein the αvβ3 antagonizing effect is the inhibition of bone resorption.

17. A method of treating or preventing osteoporosis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a compound according to Claim 1.

18. The method of Claim 12 wherein the αv integrin receptor antagonizing effect is an αvβ5 antagonizing effect.

19. The method of Claim 18 wherein the αvβ5 antagonizing effect is selected from the group consisting of inhibition of restenosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammatory arthritis, cancer, and metastatic tumor growth.

20. The method of Claim 13 wherein the αv integrin receptor antagonizing effect is a dual αvβ3/αvβ5 antagonizing effect.

21. The method of Claim 20 wherein the dual αvβ3/αvβ5 antagonizing effect is selected from the group consisting of inhibition of bone resorption, restenosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammatory arthritis, cancer, and metastatic tumor growth.

22. A method of eliciting an αv integrin receptor antagonizing effect in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 9.

23. A method of treating or preventing a condition mediated by antagonism of an αv integrin receptor in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 9.

24. A method of treating metastatic tumor growth in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a compound according to Claim 1 in combination with radiation therapy.

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US01/01953

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS COMPUTER SEARCH 1966 - TO DATE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/31061 A1 (MERCK & CO., INC) 24 June 1999, see entire document.	1-24

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
04 APRIL 2001	30 APR 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ZINNA N. DAVIS Telephone No. (703) 308-1235

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Int ional application No.
PCT/US01/01953

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

C07D 213/02, 233/04, 233/14, 233/16, 239/02, 265/36, 471/02, 487/02;
A61K 31/40, 31/44, 31/55, 31/415, 31/495, 31/505, 31/535

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

540/567; 544/105, 330, 331, 332, 333, 335, 349; 546/113, 268.1, 336, 342; 548/311.1, 349.1, 352.1; 514/215, 230.5, 248, 256, 272, 300, 336, 357, 401, 402

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

540/567; 544/105, 330, 331, 332, 333, 335, 349; 546/113, 268.1, 336, 342; 548/311.1, 349.1, 352.1; 514/215, 230.5, 248, 256, 272, 300, 336, 357, 401, 402